Remarks

Amendments to the Claims

Claim 1 has been amended to make it clearer that the matrix must be in the shape of the tissue that it is to replace, in this case, a heart valve or heart valve leaflets. Support is found at col. 3, lines 21-24; 62-63; and 66-67of the patent. The claim has also been amended to recite that the resulting cell-matrix construct can withstand repeated stress and strain. Supoort is found at col. 2, lines 40-43.

New claims 16 and 17 are drawn to specific embodiments of example 1 at col 7-8.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claim 8 was rejected under 35 U.S.C § 112, second paragraph as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 8 is dependent upon claim 5, both of which have been amended to recite "heart valve".

Rejection Under 35 U.S.C. §102

Claims 1, 2, 5, 8, 9, 15 were rejected under 35 U.S.C § 102(b) as being anticipated by U.S. Patent No. 4,902,289 to Yannas ("Yannas 1"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991).

The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.").

Claim 1 recites a method for making a cell-matrix construct for use as a heart valve comprising

implanting into an animal a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet, wherein the matrix is formed of a biocompatible, biodegradable polymer having seeded therein cells selected from the group consisting of endothelial cells, myofibroblasts, skeletal muscle cells, vascular smooth muscle cells, myocytes, fibromyoblasts, and ectodermal cells, wherein the cell-matrix construct can withstand repeated stress and strain.

Yannas 1 describes a multilayer **blood vessel** prosthesis and methods of making the prothesis. Yannas 1 does not describe a cell-matrix construct in the shape of a heart valve or leaflet as clearly defined by the claims as amended.

Rejection Under 35 U.S.C. §103

Claims 12, 13, 14 were rejected under 35 U.S.C § 103 (a) as obvious over U.S Patent No. 4,902,289 to Yannas ("Yannas" 1) and further in view of U.S Patent No. 4,505,266 to Yannas, et al. ("Yannas 2"). Claims 1-5 and 8-15 were rejected under 35 U.S.C § 103 (a) as obvious over U.S. Patent No. 3,514,791 to Sparks ("Sparks") in view of U.S. Patent No. 4,520,821 to Schmidt et al. ("Schmidt"), U.S. Patent No. 5,514,378 to Mikos ("Mikos"), or U.S. Patent No. 5,709,854 to Griffith-Cima et al. ("Griffith-Cima"). Applicants respectfully traverse these rejections.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine

reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier* , 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the describeing or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit describeings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology,* 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not

diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed.

Yannas 1 and Yannas 2

As discussed above, Yannas 1 describes a multilayer **blood vessel** prosthesis and methods of making the prothesis.

Yannas 2 describes seeding cells into a fibrous lattice in order to promote the growth of cells or the generation of tissue at a wound and has been cited for the purpose of including growth factors.

Neither Yannas 1 nor Yannas 2, alone or in combination, teaches or suggests a cell-matrix construct in the shape of a heart valve or leaflet as defined by the claims.

Sparks, Schmidt, Mikos, and Griffith-Cima

Sparks describes a die into which is placed a Dacron mesh secured to a stainless steel supporting ring (see column 5, lines 18-24). The die consists of a tube and mandrel (col. 3, lines 29-31). Figures 6-12 illustrate a die for growing a tricuspide heart valve.

Sparks does not teach or suggest a fibrous matrix formed of a biocompatible, **biodegradable** polymer and seeded with cells. Sparks relies on natural body processes to produce the necessary connective tissue to fill the die cavity and form the valve graft (see column 2, lines 27-32 and column 5, lines 32-36).

Mikos discloses preparing biocompatible porous polymer membranes by dispersing salt particles in a biocompatible polymer solution, which are removed following solidification to leave a porous structure, which can be prepared in the form of a particular structure (col. 13,

lines 43-52). There is no disclosure of heart valves or leaflets.

Schmidt discloses a bioresorbable mesh or gauze for correcting a defect in a tubular structure such as the ureter, where a single layer of cells is applied to a PLGA mesh, and the mesh implanted to repair the defect..

Griffith-Cima discloses a cell-polymeric solution, which is injected into an animal to form a polymeric hydrogel containing dispersed cells. The method is particularly well suited to formation of a bulking agent, or fill in a hole in a tissue, but cannot be used to form a structure in the shape of a heart valve or leaflet.

Sparks does not disclose a fibrous polymeric matrix in the shape of a heart valve or heart valve leaflet which is implantable; Sparks discloses a separate die to give fabric a desired structure. None of these references make up for the deficiency in Sparks by teaching or suggesting replacing the die-mandrell-fabric of Sparks with cell-matrix constructs shaped to conform to at least a part of a heart valve or heart leaflet. Therefore, a *prima facie* case of obviousness has not been established, since the references (when combined) do not teach or suggest all the claim limitations.

In addition, there is no motivation to combine these references as the Examiner has done, nor would one skilled in the art have a reasonable expectation of success if one did so, based on the art, to yield a structure which can withstand repeated stress and strain. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years.

For example, Sparks describes dies containing **stainless steel, screws, and plates** (see column 5, lines 18-31). This is completely different from the formation of tissue by injecting a

cell-polymeric **solution** that gels *in vivo* (Griffith-Cima) or preparing biocompatible porous polymer membranes by dispersing particles in a biocompatible polymer **solution** (Mikos). One skilled in the art would not be led by the combination of references to substitute a polymer solution or gel for the stainless steel structure of Sparks.

No where is there any teaching of the need for a cell-matrix structure which can resist repeated stress and strain, much less any teaching of how to achieve one. The advantages of the claimed cell-matrix constructs and methods for manufacture are quite evident from the attached articles. These articles also demonstrate that the resistance to repeated stress and strain is not inherent in the materials.

None of the art discloses, nor leads one of skill in the art to, the specific combination of new claims 16-17.

Allowance of claims 1-5 and 8-15, as amended, and new claims 16 and 17, is respectfully solicited.

Respectfully submitted,

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Note: Performing your original search, ***vacanti heart valves sheep***, in PubMed will retrieve *13* citations.

1: Circulation. 1996 Nov 1;94(9 Suppl):II164-8.

Tissue-engineered heart valves. Autologous valve leaflet replacement study in a lamb model.

Shinoka T, Ma PX, Shum-Tim D, Breuer CK, Cusick RA, Zund G, Langer R, Vacanti JP, Mayer JE Jr.

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BACKGROUND: We have previously reported the successful creation of tissue-engineered valve leaflets and the implantation of these autologous tissue leaflets in the pulmonary valve position. This study was designed to trace cultured cells that were seeded onto a biodegradable polymer with the use of a 1,1'-dioctadecyl-3,3,3' 3'-tetramethylindo-carbocyanine perchlorate (Di-1) cell-labeling method. We also examined the time-related biochemical, biomechanical, and histological characteristics and evolution of these tissue constructs. METHODS AND RESULTS: Mixed cell populations of endothelial cells and fibroblasts were isolated from explanted ovine arteries. Endothelial cells were selectively labeled with an acetylated low density lipoprotein marker and separated from fibroblasts with the use of a fluorescence-activated cell sorter. A synthetic biodegradable scaffold consisting of polyglycolic acid fibers was seeded first with fibroblasts, then coated with endothelial cells. Using these methods, we implanted autologous cell/polymer constructs in six animals. In two additional control animals, a leaflet of polymer was implanted without prior cell seeding. In each animal, cardiopulmonary bypass was used to completely resect the right posterior leaflet of the pulmonary valve and replace it with an engineered valve leaflet with (n = 6) or without (n = 2) prior cultured cell seeding. The animals were killed either after 6 hours or after 1, 6, 7, 9, or 11 weeks, and the implanted valve leaflets were examined histologically, biochemically, and biomechanically. 4-Hydroxyproline assays were performed to determine collagen content. Leaflet strength was evaluated in

vitro with a mechanical tester Factor VIII and elastin stains were done to verify histologically that endothelial cells and elastin, respectively, were present. Animals receiving leaflets made from polymers without cell seeding were killed and examined in a similar fashion after 8 weeks. In the control animals, the acellular polymer leaflets were completely degraded, with no residual leaflet tissue at 8 weeks. The tissue-engineered valve leaflet persisted in each animal in the experimental group. 4-Hydroxyproline analysis of the constructs showed a progressive increase in collagen content. Immunohistochemical staining demonstrated elastin fibers in the matrix and factor VIII on the surface of the leaflet. The cell-labeling experiments demonstrated that the cells on the leaflets had persisted from the in vitro seeding of the leaflets. CONCLUSIONS: In the tissue-engineered heart valve leaflet, transplanted autologous cells generated a proper matrix on the polymer scaffold in a physiological environment at a period of 8 weeks after implantation.

MeSH Terms:

- Animals
- Biomedical Engineering*
- Cells, Cultured
- Heart Valve Prosthesis/methods*
- Myocardium/pathology
- Research Support, Non-U.S. Gov't
- Sheep

PMID: 8901739 [PubMed - indexed for MEDLINE]

Note: Performing your original search, ***vacanti heart valves sheep***, in PubMed will retrieve *13* citations.

1: Ann Thorac Surg. 1995 Dec;60(6 Suppl):S513-6. Related Articles, Links

Tissue engineering heart valves: valve leaflet replacement study in a lamb model.

Shinoka T, Breuer CK, Tanel RE, Zund G, Miura T, Ma PX, Langer R, Vacanti JP, Mayer JE Jr.

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BACKGROUND. Valve replacements using either bioprosthetic or mechanical valves have the disadvantage that these structures are unable to grow, repair, or remodel and are both thrombogenic and susceptible to infection. These characteristics have significantly limited their durability and longevity. In an attempt to begin to overcome these shortcomings, we have tested the feasibility of constructing heart valve leaflets in lambs by seeding a synthetic polyglycolic acid fiber matrix in vitro with fibroblasts and endothelial cells. METHODS. Mixed cell populations of endothelial cells and fibroblasts were isolated from explanted ovine arteries. Endothelial cells were selectively labeled with an acetylated low-density lipoprotein marker and separated from the fibroblasts using a fluorescent activated cell sorter. A synthetic biodegradable scaffold constructed from polyglycolic acid fibers was seeded with fibroblasts, which grew to form a tissue-like sheet. This tissue was subsequently seeded with endothelial cells, which formed a cellular monolayer coating around the leaflet. Using these constructs, autologous (n = 3) and allogenic (n = 4) tissue engineered leaflets were implanted in 7 animals. In each animal the right posterior leaflet of the pulmonary valve was resected and replaced with an engineered valve leaflet. RESULTS. All animals survived the procedure. Postoperative echocardiography demonstrated no evidence of stenosis and trivial pulmonary regurgitation in the autografts and moderate regurgitation in the allogenic valves. Collagen analysis of the constructs showed development of an extracellular matrix. Histologic evaluation of the constructs demonstrated

appropriate cellular architecture. CONCLUSIONS. This preliminary experiment showed that a tissue engineered valve leaflet constructed from its cellular components can function in the pulmonary valve position. Tissue engineering of a heart valve leaflet is feasible, and these preliminary studies suggest that autograft tissue will probably be superior to allogenic tissue.

MeSH Terms:

- Animals
- Bioprosthesis*
- Culture Techniques*
- Endothelium, Vascular/cytology
- Fibroblasts/cytology
- Heart Valve Prosthesis
- Heart Valves*/surgery
- Polyglycolic Acid
- Sheep

Substances:

- Polyglycolic Acid

PMID: 8604922 [PubMed - indexed for MEDLINE]